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Therapy-induced neuroplasticity in chronic aphasia

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ABSTRACT

Research on the neural substrate of aphasia recovery has consistently increased since the advent of functional neuroimaging. The evidence from therapy-induced aphasia recovery studies shows that better recovery results from the reactivation of left hemisphere function; still, the specific left hemisphere key areas that sign successful outcome with a specific therapy approach remain to be identified. Nine participants suffering from aphasia received brief and intensive therapy with Semantic Feature Analysis (SFA). Behavioural and neuroimaging data during overt picture naming were obtained prior to and after therapy. This paper reports on a group of participants having benefited from SFA, and two distinct patterns of improvement.

Correlational analysis showed that differences in outcome were not related to lesion size, but were negatively correlated with damage to Broca's area (BA45). Moreover, a group analysis showed that therapy-induced recovery following SFA was characterized by (a) a significant correlation between improvement and activation in the left precentral gyrus (BA4/6) before therapy, and (b) the recruitment of the left inferior parietal lobule, an area known for its role in semantic integration, following therapy with SFA. Individual fMRI analyses showed that although adaptive brain plasticity appeared to operate differently in each patient, best responders to SFA therapy recruited less areas after training compared to participants having shown less recovery who showed a larger number of activated areas sustaining recovery. The results of the present study suggest that a significant activation of BA4/6 could indicate the use of SFA to achieve successful outcome. Also our results suggest that greater SFA improvement in chronic aphasia is associated with recruitment of areas in the left hemisphere.

1. Introduction

Despite the availability of a wide range of neuroimaging techniques, it is still difficult to predict the outcome of aphasia following a stroke (Pedersen, Vinter, & Olsen, 2004). Many patients will recover rapidly after the lesion in the phases known as acute and sub-acute. However, language recovery is minimal for others during the same time period, and a relatively severe aphasia may persist one year after brain insult. According to Wade, Hewer, David, and Enderby (1986), one in eight stroke survivors will present with persistent chronic aphasia. In addition, among the patients who initially suffered from aphasia, two in five will still present with aphasia one year after stroke; this represents so-called chronic aphasia (Pedersen et al., 2004). In the past, intensive language therapy was considered to be efficient only with acute and sub-acute patients. However, several recent studies have shown that intensive language therapy is associated with language improvements even in chronic aphasia (Cornelissen et al., 2003; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Fridriksson et al., 2007; Meinzer, Streiftau, & Rockstroh, 2007; Peck et al., 2004; Vitali et al., 2007).

The potential of aphasia therapy to trigger recovery is limited by a number of factors, such as the initial severity (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995) and the size and location of the lesion (Basso, 1992). Of these two factors, the role of

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lesion size has been examined more extensively. Specifically, a significant relationship between lesion size and aphasia severity has been reported when both cortical and subcortical areas were damaged (Demeurisse & Capon, 1987). However, when the lesion was restricted to cortical areas, aphasia outcome could not be predicted (Demeurisse & Capon, 1987; Lazar, Speizer, Festa, Krakauer, & Marshall, 2008; Naeser, Helm-Estabrooks, Haas, Auerbach, & Srinivasan, 1987). Thus, smaller lesions that include core language areas have shown to induce more severe language impairments than larger lesions elsewhere and are better predictors of aphasia recovery (Naeser & Palumbo, 1994). For example, Naeser et al. (1987) reported that lesions in Wernicke's area and beyond the middle temporal gyrus (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004) produced more severe and more persistent comprehension impairments than more widespread brain damage in other areas. Greater improvements after therapy were associated with smaller volume loss in the hippocampus, whereas no correlations were detected between therapy-related improvement and lesion size (Meinzer et al., 2010). Parkinson, Raymer, Chang, Fitzgerald, and Crosson (2009) investigated the relationship between lesion size and naming abilities and reported that larger lesions in anterior areas were associated with better naming abilities and greater improvement after therapy, which supported previous findings (Vitali et al., 2007; Zahn et al., 2004). This suggests that the brain mechanisms underlying aphasia recovery are complex and are determined by multiple factors (Lazar et al., 2008) that have not yet been fully explored.

Recently, the advent of functional neuroimaging techniques has greatly contributed to our understanding of therapy-induced brain plasticity in aphasia. Neuroplasticity is a concept that refers to the brain's potential to modify neural circuits. This potential is reflected not only during development (developmental neuroplasticity) but also throughout the lifespan and following brain damage. In the latter case, two types of plasticity have been described: functional reactivation and functional reorganization. Functional reactivation implies a functional recovery of perilesional classical language areas in the left hemisphere (LH) (Cappa, 2000; Heiss, Thiel, Kessler, & Herholz, 2003), and has been associated with better outcomes (Heiss & Thiel, 2006; Rosen et al., 2000; Saur et al., 2006). Functional reorganization consists in the activation of non-classical language areas, either perilesional areas in the LH (Karbe, Kessler, Herholz, Fink, & Heiss, 1995; Léger et al., 2002; Warburton, Price, Swinburn, & Wise, 1999) or right hemisphere (RH) areas homologous to the damaged areas, which can be recruited when there is permanent damage to the LH language processing areas (Crinion & Price, 2005; Musso et al., 1999; Pizzamiglio, Galati, & Committeri, 2001; Pulvermüller et al., 2001; Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005; Rosen et al., 2000; Sharp, Scott, & Wise, 2004; Weiller et al., 1995). Thus, some research groups associate recovery with neuroplastic changes in the LH (Cornelissen et al., 2003; Fridriksson, Baker, & Moser, 2009; Meinzer et al., 2008), whereas others report recovery following functional reorganization in the RH (Crosson et al., 2005; Peck et al., 2004), and still others argue that therapy-induced recovery from aphasia relies upon bilateral neuroplasticity (Fridriksson et al., 2006, 2007).

In view of this disparity, there has been growing interest in the role of both the LH and RH in the recovery from aphasia. A recent review of the literature shows a lack of convergent results of this research, highlighting the roles of both cerebral hemispheres in aphasia recovery (Meinzer, Harnish, Conway, & Crosson, 2011). Although some studies associate language improvement with RH activations (Thulborn, Carpenter, & Just, 1999; Winhuisen et al., 2005), the role of the RH in aphasia recovery remains controversial. For instance, Belin et al. (1996) suggested that the recruitment of the RH was maladaptive and could harm language recovery in the LH, which could lead to the persistence of linguistic deficits. In line with this perspective, Naeser et al. (2005) used repetitive transcranial magnetic stimulation (rTMS) to inhibit the right pars triangularis. The authors reported improved oral naming in a severe non-fluent global aphasic patient and argued that their findings provided evidence of a maladaptive functional reorganization involving the RH. In another study, Winhuisen et al. (2005) used rTMS on the inferior frontal gyrus (IFG) bilaterally in subacute aphasic patients. As opposed to patients who experienced interference when rTMS was applied to both the left and right IFG, participants for whom the stimulation only triggered interference when applied to the left IFG performed significantly better 10 days after suffering from their stroke. However, in their follow-up study, Winhuisen et al. (2007) reported equivalent improvement in two participants who showed significant bilateral interference of the IFG eight weeks after their stroke. These results suggest that RH activation might not be a negative factor for prognosis and that the RH's potential for adaptive neuroplasticity needs further exploration.

If the role of the RH is still controversial, it is relatively widely acknowledged that the recruitment of the LH seems to be associated with better recovery from aphasia. In this regard, a recent study by van Oers et al. (2010) reported a positive correlation between the activation of the left IFG and improved picture and sentence naming. Accordingly, robust correlations between post-therapy aphasia recovery and significant activations in the LH language areas have been reported consistently (Breier et al., 2004; Cao, Vikingstad, George, Johnson, & Welch, 1999; Crinion & Price, 2005; Heiss & Thiel, 2006; Meinzer et al., 2008), suggesting that better language recovery is associated with LH activations. In line with this view, Baker, Rorden, and Fridriksson (2010) applied transcranial direct-current stimulation on left frontal areas and showed better naming improvements when this was combined with computerized language therapy.

In summary, research on therapy-induced neuroplasticity in aphasia recovery has increased considerably in the last years. Most studies have adopted a multiple single-case perspective; more recently, a few group studies have been published (Fridriksson, 2010; Meinzer et al., 2008; van Oers et al., 2010). On the one hand, multiple single-case studies have the advantage of accounting for individual differences, while on the other hand, research with individuals who share common symptoms (e.g., severe anomia), or group studies, has the advantage of allowing for generalization and may demonstrate the efficacy of the therapy (Basso, 2003). Therefore, in the present study, we used a combination of multiple single-case and group studies to investigate the recovery from chronic aphasia and to better understand both individual differences and the common areas recruited by a specific therapy.

Thus, the purpose of the present study was to identify the neuroplastic changes associated with therapy-induced recovery from chronic aphasia following Semantic Feature Analysis (SFA) therapy (Boyle & Coelho, 1995; Ylvisaker & Szekeres, 1985). Nine participants with moderate to severe chronic aphasia were evaluated during two pre-/post-therapy event-related functional magnetic resonance imaging (fMRI) sessions. In addition, activation maps associated with oral naming performance were obtained before and after three weekly sessions of therapy. SFA sessions lasted for a maximum of six weeks, or until participants were able to name 80% of the trained items in two successive therapy sessions. Given the extended lesions and the severity of aphasia, we hypothesized that (1) successful naming improvement following SFA would be associated with the significant activation of a bilateral network, and (2) the greatest improvements in naming would be associated with a significant reactivation of perilesional areas in the LH.

2. Materials and methods

2.1. Participants

Nine participants with chronic aphasia (4 women; mean age: 62 ± 6.0 years) took part in the study. All nine patients were considered to have chronic aphasia because all had suffered from stroke at least 48 months prior to the study (mean time post-onset: 110.2 ± 92.5 months). Demographic information on the whole sample is presented in Table 1. Aphasia severity and typology were determined by an experienced speech-language pathologist (SLP; KM). Inclusion criteria were: (1) a single LH stroke; (2) a diagnosis of moderate to severe aphasia, according to the Montreal-Toulouse battery (Nespoulous et al., 1986); (3) the presence of anomia in a standardized naming task (Snodgrass & Vanderwart, 1980); (4) having French as their mother tongue; and (5) being right-handed prior to the stroke (Edinburgh Inventory, Oldfield, 1971; mean handedness: 93.3 ± 8.6). Exclusion criteria were: (1) the presence of a neurological or psychiatric diagnosis other than stroke; (2) incompatibility with fMRI testing; or (3) diagnosis of mild cognitive impairment or dementia prior to stroke. Participants gave written informed consent according to the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Regroupement de Neuroimagerie/Québec.

2.2. Experimental procedure

The experimental protocol is similar to that of a previous study carried out by our research group (Marcotte & Ansaldo, 2010). Briefly, a baseline language assessment was conducted prior to therapy, followed by an initial fMRI session (T1), which served to identify the neural substrate of spontaneous correct naming. Afterwards, patients received SFA therapy from a trained SLP. A second fMRI session (T2) was performed when participants achieved 80% performance on treated items or at a maximum of six weeks. This second fMRI session allowed us to identify brain areas that subserved therapy-induced neuroplasticity. During both fMRI sessions, patients performed an overt naming task.

2.3. Complete language assessment

Before SFA therapy, all participants were examined with the Montreal-Toulouse 86 Beta version (Nespoulous et al., 1986), which allows for the description of aphasia profiles. Also before therapy, all participants underwent two baseline naming assessments using 260 object images (Snodgrass & Vanderwart, 1980). Both baselines were separated by a one-week interval; all participants showed stable oral naming performance ($W(8)=23.5$, $p=.905$).

2.4. fMRI sessions: Stimuli and procedure

Before the first fMRI session, all participants underwent a practice session in the mock scanner so they could become accustomed to the scanner noise and environment. In this way, stressful situations caused by the fMRI were minimized and a decrease in participant performance might be avoided (LaPointe, 2005). During the practice session, the task was the same as the one used during the fMRI session, so participants would be familiar with the sequence. However, the stimuli used during the fMRI session were different.

Stimuli for the naming task were color pictures from the Hemera© set (www.hemera.com) presented on a white background. Digitally distorted images of the same pictures were used for the control condition ($n=20$). In order to provide more individualized therapy, stimuli for SFA therapy were selected on the basis of individual performance on the Snodgrass and Vanderwart naming task (Snodgrass & Vanderwart, 1980). The pictures presented were different for each participant

Table 1
Patient characteristics, language evaluations and therapy results.

Patient information	P01[a]	P02[a]	P03[a]	P04[a]	P05[b]	P06[a]	P07[b]	P08[b]	P09[b]
Age (years)	67	67	66	55	50	67	62	63	64
Sex	M	M	M	M	F	F	M	F	F
Time post-stroke (months)	72	54	241	61	65	300	72	77	50
Education (years)	20	15	12	12	12	12	17	22	12
Lesion volume (cm^3)	167.84	117.84	84.77	14.55	64.16	172.21	118.39	295.76	215.31
Lesion location	Frontal, parietal, temporal	Frontal, temporal	Frontal, temporal	Frontal	Frontal, temporal, insula	Frontal, parietal, temporal, insula	Frontal, temporal, occipital, insula	Frontal, parietal, temporal	Frontal, temporal, insula
Pre-therapy language assessment									
Comprehension (max. 47) (MT-86)	42	41	39	41	40	43	35	21	26
Repetition (max. 33) (MT-86)	27	27	28	27	23	25	24	1	9
Evocation (MT-86)	6	4	12	5	2	12	6	0	4
Naming (max. 260) (Snodgrass & Vanderwart) (first)	200	128	156	152	54	187	86	50	28
Naming (max. 260) (Snodgrass & Vanderwart) (second)	199	120	158	160	53	189	84	47	30
Aphasia and speech profile (according to MT-86)	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Wernicke's aphasia and AoS	Broca's aphasia and AoS
Severity	Moderate	Moderate to severe	Moderate to severe	Moderate to severe	Severe	Severe	Moderate to severe	Severe	Severe
Post-therapy language assessment									
Comprehension (max. 47) (MT-86)	42	41	40	41	40	39	38	23	26
Repetition(max. 33) (MT-86)	30	27	28	28	23	23	25	7	9
Evocation (MT-86)	7	5	14	7	3	14	8	1	4
Naming (max. 260) (Snodgrass & Vanderwart)	241	157	201	198	70	210	100	65	55
Language Training Results									
Trained objects (%)	100	85	80	90	80	90	80	60	60
Untrained objects (%)	20	25	20	35	25	20	15	17.5	20
Therapy length (# sessions)	9	11	9	9	18	9	14	18	18

[a] Most successful responders.
[b] Less successful responders. AoS=Apraxia of speech.

after the stimuli had been selected in an individualized manner. Based on this rationale, two sets of items were created for each participant: correctly named (spontaneous, $n=20$) and incorrectly named ($n=60$). Of the 60 incorrectly named items, only 20 were trained, and the remaining 40 items allowed us to measure generalization of therapy effects to untrained items. All sets of items (spontaneous, trained and untrained) were matched for number of phonemes, word frequency and syllabic complexity. Statistical analysis for all nine participants showed no significant differences between the three word lists regarding these variables. As well, the Snodgrass and Vanderwart set of words is divided into nine different semantic categories; given that each participant produced different errors, it was not possible to balance the N of items across all nine semantic categories, for all nine patients. In the pre-therapy fMRI session (T1), all sets of items (spontaneous, trained and untrained) were presented to the participants, as were the control items (distorted items). After therapy (T2), the same items were presented.

Participants lay supine on the MRI scanner bed with their head stabilized by foam. Stimuli were randomly projected by means of Presentation software v.10.0 (www.neurobs.com) from a computer onto a screen at the head of the bore, and were visible in a mirror attached to the head coil. Each picture was presented for 4500 ms, with an interstimulus interval (ISI) ranging from 4325 ms to 8500 ms. Participants were instructed to name each picture, as clearly and accurately as possible, and to say 'baba' each time they saw a distorted picture, while avoiding head movements. An MRI-compatible microphone was placed close to the participant's mouth and Sound Forge software (www.sonycreativesoftware.com) was used to record oral responses.

2.5. Imaging parameters

Images were acquired using a 3 T MRI Siemens Trio scanner, with a standard 8-channel head coil. The image sequence was a T2*-weighted pulse sequence (TR=2200 ms; TE=30 ms; matrix=64 × 64 voxels; FOV=192 mm; flip angle=90°; slice thickness=3 mm; acquisition=36 slides in the axial plane, with a distance factor of 25%, so as to scan the whole brain, including the cerebellum). A high-resolution structural image was obtained before the two functional runs using a 3D T1-weighted pulse sequence (TR=2300 ms; TE=2.91 ms; 160 slices; matrix=256 × 256 mm; voxel size=1 × 1 × 1 mm; FOV=256 mm).

2.6. Language therapy with SFA

A trained SLP provided the SFA therapy, which lasted for an hour and was provided three times a week. During each session, participants were trained to name 20 objects. If the participant could not name the object within 5–10 s, a series of semantic prompts corresponding to the semantic features of the target (Boyle & Coelho, 1995) were given in the form of questions by the SLP. For instance, with the word watering can, the following prompts could be used: To which category does it belong? Where do we usually see this? What do we do with it? After three prompts, the word was provided to the participant, who was asked to repeat it once.

2.7. Data analyses

2.7.1. Behavioural data

Correct responses on the naming task were computed prior to and after therapy. Responses to the fMRI naming task were recorded and coded off-line by an experienced SLP (KM) according to a pre-established procedure. Specifically, responses were scored according to a list of correct expected responses, which was drawn up prior to the study by two experienced SLPs (KM and AIA). Responses were rated as 'correct' only if they corresponded to an expected word. Otherwise, the response was considered 'incorrect'. A second rater, blind to the experiment, also scored the responses, and there were no instances of disagreement.

Following therapy, accuracy was calculated with trained and untrained stimuli, the latter allowing us to test the generalization of therapy effects to untreated items. The degree of improvement was calculated by reference to the number of correctly named trained items after therapy (non-parametric analysis; Wilcoxon test). Given the state of knowledge regarding the impact of lesion size on prognosis, we also explored the possibility that the degree of recovery could be related to lesion size. Thus, a Spearman correlation between lesion size and post-therapy improvement was computed. Moreover, Spearman correlations were calculated between a variety of scores in the pre-therapy language assessment, and therapy outcome, so as to identify those language abilities that could best predict improved naming following SFA.

2.7.2. Patient lesion-deficit mapping

A qualitative lesion-symptom analysis with voxel-lesion symptom mapping (VLSM; Bates et al., 2003) was performed. First, a lesion overlap image was constructed for all nine participants using MRIcron (version of 1 April 2010) software (Rorden, Karnath, & Bonilha, 2007; www.mricro.com/mricron). Given the group size, a nonparametric Brunner-Munzel (BM) test (Brunner & Munzel, 2000) was used to control for multiple comparisons (Nichols & Holmes, 2002) and to reduce type I errors (Medina, Kimberg, Chatterjee, & Coslett, 2010). This test was implemented in non-parametric mapping (version of 1 April 2010) software (Rorden et al., 2007; www.mricro.com/npm), which allowed for the permutation of the derived correction. Statistical comparisons were made for each eligible voxel; only voxels affected in at least four cases out of nine were included. Fig. 1 shows the lesion coverage in our sample and indicates the regions where VLSM could test for potential lesion–behaviour relationships. BM tests were performed at each eligible voxel, with the degree of improvement in therapy entered as a continuous and dependent variable.

Preprocessing and statistics were performed using SPM5. Preprocessing included slice timing, realignment, segmentation, normalization and smoothing by using a spatially smoothed 10-mm Gaussian filter. Analyses were performed to separate BOLD responses for each trial type (i.e., responses associated with spontaneous object naming and trained object naming). Phonological and semantic paraphasias, as well as correct naming of untrained objects after therapy, were modelled separately; however, the number of items per paraphasia type was insufficient for further analyses. For each subject, task-related BOLD changes were examined by convolving a vector of naming onset with the haemodynamic response function (HRF) and its temporal derivative.

Preprocessed data were analysed using the general linear model implemented in SPM5. Statistical parametric maps were obtained for each individual subject, by applying linear contrasts to the parameter estimates for the events of interest; this resulted in a t-statistic for every voxel. Neuroimaging data analyses were performed only on correct responses. Individual maps and group averages were calculated for each condition of interest by employing a one-sample t-test without constant term (random effects) on the resulting contrast image. Main contrasts (Naming vs. Baba) were performed with cluster size (k) superior to 10 voxels and $p<.005$ uncorrected.

In order to explore the brain regions associated with being more successful after SFA therapy (i.e., being able to name more trained items following therapy) as a function of time, correlations between the BOLD signal and the number of trained objects correctly named after training (i.e., improvement) were calculated

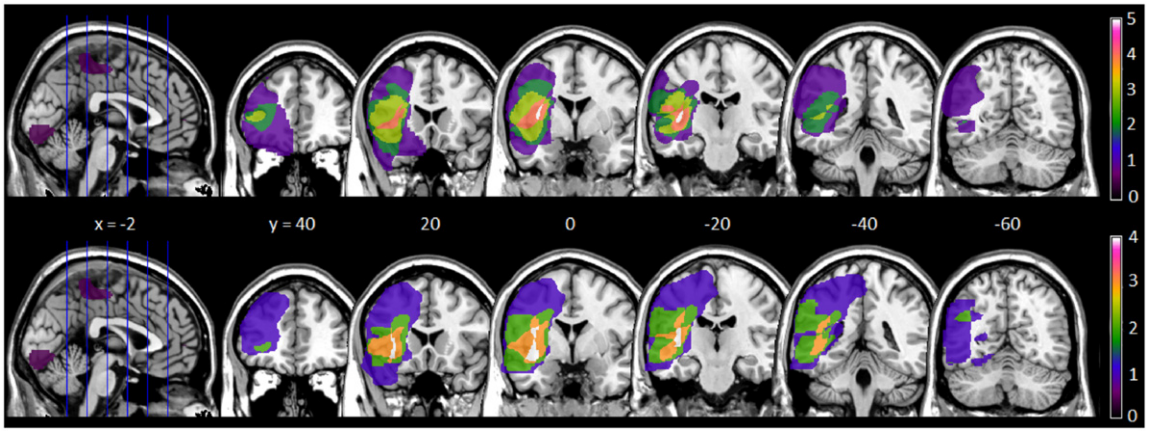

Fig. 1. Lesion overlay plot: On the upper section, lesion size averaged for all five Most Successful Responders (MSR) superimposed on a standard brain template. On the lower section, lesion size averaged for all four Less Successful Responders (LSR). Orange and white colors indicate the number of subjects that do share a lesion in a specific brain area in each group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

both before and after therapy. Thus, correlations between the improvement in naming and its HRF signal amplitude in the contrast (Spontaneous Object $Naming_{T1}$–$Baba_{T1}$) were gathered in order to identify the areas that could predict the best responders to SFA therapy. Correlations between improved naming and the contrast (Trained Object $Naming_{T2}$–$Baba_{T2}$) were determined in order to identify brain areas that were specifically recruited by therapy. Furthermore, signals from cluster maxima were extracted and non-parametric correlation analyses (Spearman rank, SPSS® v19.0) were computed between signal values and naming improvement in order to obtain a more conservative estimation of these effects. Only the results of correlations that remained significant after these analyses are reported.

3. Results

3.1. Behavioural results

As described previously, both 'treated' and 'untreated' items were incorrectly named items at the baseline behavioural assessments. Consequently, naming accuracy at the first fMRI session was 0% with both lists. Improvement following SFA therapy was measured using the number of trained objects that participants were able to correctly name during the second fMRI session (T2). All participants benefited from SFA therapy, with a mean improvement of 80% ± 13.3. These gains were obtained after 3 to 6 weeks of intensive SFA therapy, with a mean of 4.3 weeks and an average of 12.7 ± 4.2 therapy sessions. All participants showed some degree of generalization of SFA effects to untrained material. Specifically, at the group level ($n=9$), the mean improvement with untrained stimuli was 21.3% ± 5.8 as compared to 80% ± 13.3 with trained items (see Table 1). Still, the difference in improvement with trained and untrained items was statistically significant ($W(16)=-2.67$, $p=.008$).

When considering the improvement in naming and the number of sessions together, two profiles of 'therapy responders' emerged. Specifically the most successful responders to therapy (MSR, participants P01, P02, P03, P04 and P06, see Table 1) achieved a mean improvement of 89% ± 7.4 in an average of 9.4 ± 0.9 sessions, whereas the least successful responders to therapy (LSR; participants P05, P07, P08 and P09, see Table 1) reached a mean 70% ± 11.5 improvement in an average of 17 ± 2.0 sessions. A statistical analysis allowed for the verification of these differences between the two groups in terms of improvement and therapy length. The two groups differed significantly in terms of improvement with trained items ($U=1$, $n_1=5$, $n_2=4$, $z=-2.262$, $p=.024$) and mean therapy length ($U=20$, $n_1=5$, $n_2=4$, $z=2.606$, $p<.005$). However, the degree of generalization of therapy effects to untrained items did not differ across the groups ($U=5$, $n_1=5$, $n_2=4$, $z=-1.285$, $p=.286$); it was 25% ± 6.1 for the MSR and 18.3% ± 2.4 for the LSR group.

The Spearman's correlation between lesion size and post-therapy improvement showed no relationship between lesion size and more or less successful outcome ($r=-0.368$, $p=.330$). Conversely, strong correlations between post-SFA outcome and pre-intervention language abilities were observed. Positive correlations between post-SFA improvement and pre-therapy naming scores (Snodgrass & Vanderwart, 1980) ($r=0.881$, $p=.002$), as well as sentence comprehension scores ($r=0.940$, $p<.001$), were found. A similar correlation between post-SFA improvement and word repetition scores was also found ($r=0.670$, $p=.049$), but would not survive a Bonferroni correction.

In addition to improvement, we also measured naming accuracy during both fMRI sessions. During the first fMRI session, the mean accuracy score with items that were correctly named at baseline (Snodgrass and Vanderwart picture set) was 85% ± 15. The mean accuracy score for the control condition ('Baba') was 88,3% ± 13,3. Thus, there were no significant differences in naming each category of word ($W(8)=-1.089$, $p=.276$). During the second fMRI session, the mean accuracy score of the treated items was 80% ± 13.3, whereas the mean accuracy score of the control condition was 90% ± 14.1. There was a significant difference between scores in the control condition and the treated condition ($W(8)=2.388$, $p=.017$).

3.2. Patient lesion-deficit mapping results

The lesion-deficit analysis revealed that a lesser degree of naming improvement was strongly and negatively correlated with damage to the left IFG (BA45; MNI: −31, 28, 2; $Z=3.89$) and this effect survived a 1% false discovery rate to control for multiple comparisons.

3.3. fMRI results

3.3.1. Group results

To further identify the brain regions associated with correct naming after SFA, a second-level of analysis was performed. Fig. 2 (Section A) shows all significantly activated areas at the group level ($p<.005$, $k>10$). Prior to therapy, these brain regions comprised the right precentral gyrus (PCG) and the left middle frontal gyrus (MFG), both corresponding to BA6, as well as the left middle occipital gyrus (BA19). Following SFA therapy, the only area still showing significant activation was the left inferior parietal lobule (IPL) (BA40).

In order to better relate activation patterns to behavioural improvement, a correlational analysis between cerebral activation and the degree of improvement was performed on the contrasts (Spontaneous Object $Naming_{T1}$–$Baba_{T1}$) and (Trained Object $Naming_{T2}$–$Baba_{T2}$). These analyses helped identify brain areas in which significant activations correlated with recovery, both pre- and post-therapy (see Fig. 2, Sections B and C). The significant pre-therapy activations that positively correlated with recovery following SFA therapy included the left PCG (BA4/6), right postcentral gyrus (BA3), right superior frontal gyrus (SFG, BA8), right thalamus, left medial frontal gyrus (MedFG, BA6) and left anterior cingulate gyrus (BA32). A positive correlation was observed between significant post-SFA activation of the left PCG (BA4/6) and naming improvement following therapy.

3.4. Individual results related to naming improvement

3.4.1. Pre-therapy adaptive plasticity

Considering the two distinct patterns that 'emerged' from the behavioural data, further fMRI analyses focused on individual patterns related to both MSR and LSR. For each participant within each group, voxels with the highest *Z*-scores are listed in Table 2. In the case of MSR, pre-therapy adaptive plasticity was reflected by significant activations in the left PCG (BA4/6), the superior frontal gyrus bilaterally (BA6/9), the bilateral superior and inferior temporal gyri (STG and ITG, BA38/22 and BA37/19), the left IPL (BA40) and the right middle temporal gyrus (MTG, BA21/39). Significant activations were also observed in the left parahippocampal gyrus (BA20/30), the right cuneus (BA18/19) and the cerebellum. Regarding the LSR group, pre-therapy activation patterns included significant bilateral activations in the lingual gyrus (BA17/18), as well as significant activations in the left MTG (BA39) and the left PCG (BA9). Within this group, two participants (P08, P09) showed no significant activations prior to therapy, when the correctly named items were contrasted with the distorted images.

3.4.2. Therapy-induced neuroplasticity

Regarding therapy-induced neuroplasticity, detailed activations are listed in Table 3. Four out of five of the MSR (P01, P02, P03 and P06) showed fewer and/or smaller activated clusters

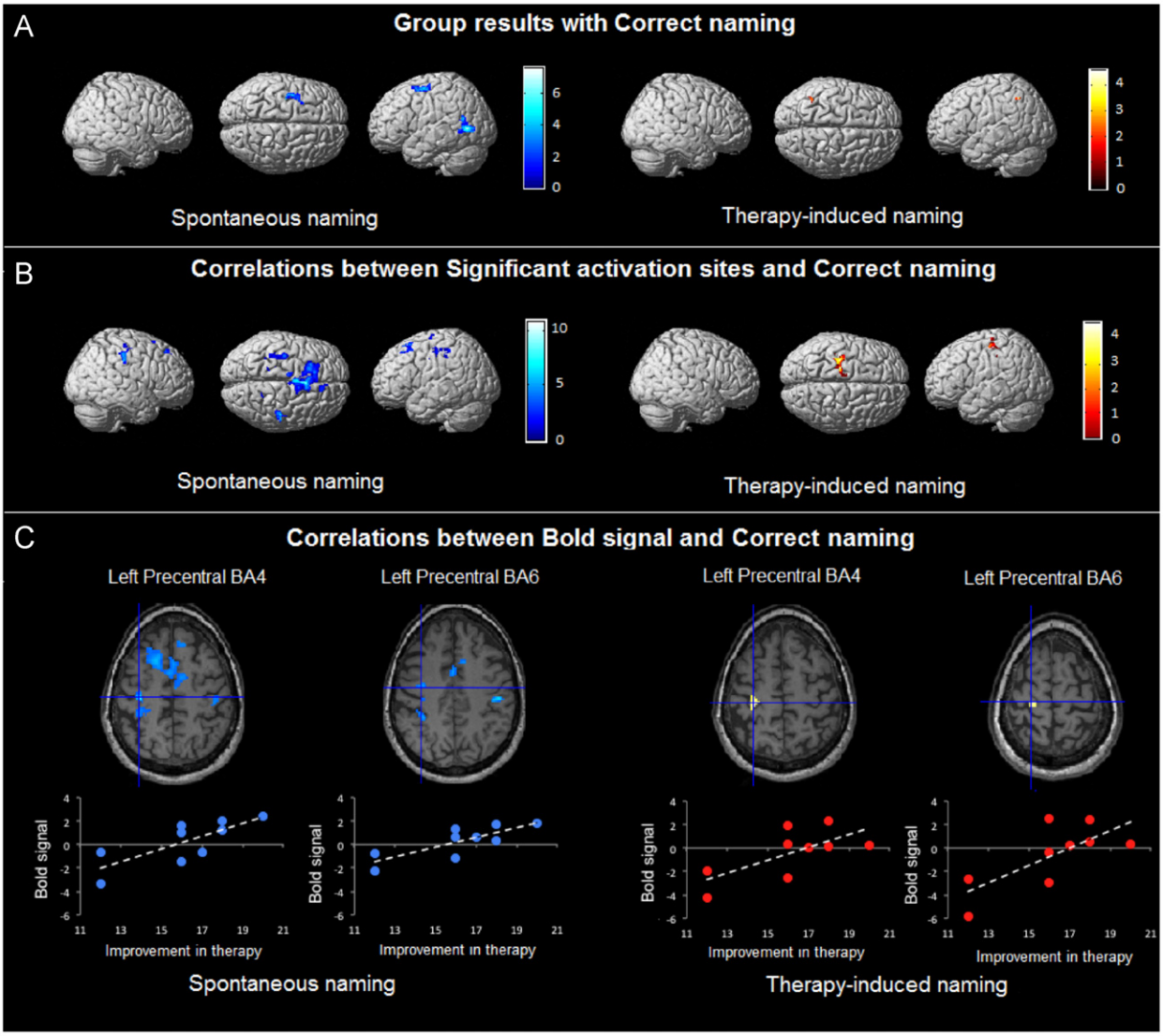

Fig. 2. Group activations maps (A) and correlational analysis with improvement (B), (C), before SFA therapy (left side) and after SFA therapy (right side) ($k > 10$, $p < 0.001$). Color-coding reflects t-values and therapy moments. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

after therapy compared to their pre-therapy activation maps. Conversely, the LSR group showed more significantly active areas after therapy than before it. The MSR group showed significant activations in the left PCG (BA4/6), the right PCG (BA6), the left IPL (BA40) and the MTG bilaterally (BA21). In one participant, the inferior frontal gyrus (BA44) was also significantly activated. With regard to LSR, therapy-induced neuroplasticity was reflected by the significant activation of occipital areas, including the right cuneus and precuneus (in two participants only; P05, P09) the left supramarginal gyrus (BA40), as well as the left MTG (BA39), the right STG (BA22), and the MedFG bilaterally (BA6/10). As was the case with the MSR group, two participants in the LSR group (P05, P07) showed significant activation in the left PCG (BA6).

4. Discussion

The purpose of this work was to explore brain plasticity mechanisms associated with intensive SFA therapy in a group of patients presenting with moderate to severe chronic aphasia. Our results showed that SFA therapy led to positive results in a group of nine patients who had concomitant neuroplastic changes, even many years after their stroke. Correlational analyses showed that SFA outcome was negatively correlated with damage to Broca's area (BA45), whereas no relation was found with lesion size. Moreover, the group analysis revealed a significant correlation between improved naming and activation in the left precentral gyrus (BA4/6), both before and after therapy. The neuroplastic recruitment of the left inferior parietal lobule might reflect the semantic nature of the therapy. The individual fMRI analyses showed two patterns of responders; the best responders to SFA therapy recruited fewer brain areas after training, as compared to the least successful responders, who recruited a larger number of activated areas to sustain improvement. Thus, by using both group and single-case analyses, the present study provides complementary results that allow for better comprehension of the neural substrate of SFA therapy in chronic aphasia.

As discussed by Fridriksson, Bonilha, Baker, Moser, and Rorden (2010), the type of analysis employed might be crucial in explaining the differences reported between studies that have addressed therapy-induced brain plasticity. On the one hand, group analyses using whole-brain templates have statistical limitations in brain areas where more than one patient has a lesion. On the other hand, Volume of Interest (VOI) and Region of

Table 2
Significant activated areas before SFA therapy for each patient with aphasia ($k > 10$, $p < .001$).

Most successful responders													
Left							**Right**						
Regions	**BA**	***x***	***y***	***z***	**T-score**	**Cluster size**	**Regions**	**BA**	***x***	***y***	***z***	**T-score**	**Cluster size**
Spontaneous naming													
Participant 1													
Inferior temporal gyrus/Fusiform	37	−44	−72	−6	4.11	1081	Superior frontal gyrus	6	4	−12	80	4.56	37
Cerebellum (culmen)		−8	−28	−26	3.60	411	Middle temporal gyrus	39	54	−56	−14	4.13	23
Precentral gyrus	4	−38	−30	76	3.19	13	Postcentral gyrus	7	4	−54	78	3.19	19
Precentral gyrus	4	−42	−14	62	2.94	11	Thalamus		18	−34	2	3.10	24
Parahippocampal gyrus	20	−14	−50	0	2.92	12	Inferior temporal gyrus	19	48	−72	−8	3.00	31
Precentral gyrus	4	−18	−28	64	2.80	16	Medial frontal gyrus	6	10	−20	58	3.00	11
Precentral gyrus	6	−42	−12	52	2.72	18	–	–	–	–	–	–	–
Parahippocampal gyrus	30	−14	−50	0	2.92	12	–	–	–	–	–	–	–
Precentral gyrus	4	−18	−28	64	2.80	18	–	–	–	–	–	–	–
Precentral gyrus	6	−42	−12	52	2.78	18	–	–	–	–	–	–	–
Participant 2													
Angular gyrus	39	−50	−70	34	4.03	851	Cerebellum (pyramis)	–	12	−68	−50	4.01	1490
Inferior parietal lobule	40	−68	−30	28	3.57	218	Cingulate	31	4	−42	−44	2.98	52
Thalamus		−14	−10	4	3.23	40	Cerebellum	–	34	−58	−18	2.91	19
Supramarginal gyrus	40	−64	−50	34	3.15	78	–	–	–	–	–	–	–
Participant 3													
Precentral gyrus	44	−62	18	2	6.07	1914	Superior frontal gyrus	6	8	−2	74	3.89	338
Precentral gyrus	4	−44	−16	42	4.91	1630	Caudate	–	20	−22	−8	3.74	109
Middle/superior frontal gyrus	6	−20	−2	68	4.37	1080	Cuneus	19	8	−94	34	3.45	13
Cingulate		−18	6	30	3.90	145	Precentral gyrus	6	54	−12	32	3.07	87
Globus pallidus		−22	−10	−6	3.68	19	Middle occipital gyrus	19	48	−56	−14	2.96	5
Superior temporal gyrus	38	−44	24	−34	3.23	19	Transverse gyrus	41	34	−28	4	2.80	7
Superior frontal gyrus	9	−38	36	32	3.09	19	Middle temporal gyrus	21	64	−10	−14	2.78	5
Parahippocampal gyrus	36	−44	34	−14	2.86	10	Superior frontal gyrus	6	18	4	68	2.70	7
Inferior parietal lobule	40	−44	−52	66	2.84	6	–	–	–	–	–	–	–
Participant 4													
							Postcentral gyrus	40	68	−28	16	3.68	41
							Superior temporal gyrus	22	64	−6	4	3.68	95
Participant 6													
							Cuneus	18	4	−92	14	3.59	173
Less successful responders													
Spontaneous naming													
Participant 5													
Lingual gyrus	18	−10	−78	4	3.66	106	Putamen		28	−14	4	3.84	184
Middle temporal gyrus	39	−44	−64	16	3.04	28	Lingual gyrus	17	20	−76	2	3.77	220
							Cerebellum	–	8	−34	−12	2.90	19
Participant 7													
Precentral gyrus	9	−40	6	42	2.87	26							
Participant 8													
No significant cluster													
Participant 9													
No significant cluster													

Interest (ROI) analyses also have major issues because crucial areas may not be included in the selection of the VOIs and ROIs. Finally, when using single- or multiple-single-case studies, it is difficult to generalize the results to the population. Interestingly, our fMRI data analyses combined a group with an individual approach to enhance our comprehension of the impact of SFA on our group of participants. Considering that this is the first study that has looked closely at the impact of SFA therapy at the neural level, single-case studies are still important to gain a better understanding of brain areas that may be recruited in some individuals and that may be crucial for their recovery. Single-case analyses may account, at least in part, for the limitations of the whole group analysis and are more appropriate in exploring perilesional activations (Postman-Caucheteux et al., 2010). Pouratian and Bookheimer (2010) recently suggested that both group and individual analyses will answer different clinical questions in the near future, when fMRI is expected to be used in clinical settings. Whereas group analyses have the potential to highlight brain regions that may be essential when trying to predict which individual could benefit from a specific therapy, individual analyses are optimal when aiming to target the location of a particular function, such as naming. For these different clinical purposes, the use of both analyses provides a more complete understanding of therapy-induced plasticity in chronic aphasia.

Group analyses showed that post-therapy adaptive plasticity included the left IPL (BA40), an area known for its contribution to the integration of semantic information and its coupling with phonological information (Lau, Phillips, & Poeppel, 2008). This result led us consider that participants had in fact learned a semantic strategy that supported word retrieval. Moreover, the left IPL has been associated with the integration of word features and semantic categorization (Chou et al., 2006). This result is interesting considering that SFA boosts semantic representations in order to facilitate phonological retrieval. Given the number of participants in the present study, it is evident that more research is still needed in this field, but we can hypothesize that the left IPL plays a crucial role in SFA therapy.

Ultimately, the goal of studying the impact of language therapy on aphasia is to predict and identify who would benefit most from a specific therapy. To date, few studies have tried to identify brain

Table 3
Significant activated areas after SFA therapy for each patient with aphasia ($k > 10$, $p < .001$).

Most successful responders													
Left							**Right**						
Region	**BA**	***x***	***y***	***z***	**T-score**	**Cluster size**	**Region**	**BA**	***x***	***y***	***z***	**T-score**	**Cluster size**
Therapy-induced Naming													
Participant 1													
Thalamus	–	−22	−20	8	3.34	24	Middle temporal gyrus	21	60	−40	−6	2.81	21
Participant 2													
Superior frontal gyrus	6	−4	10	56	3.82	196	Postcentral gyrus	2	12	−68	−50	4.01	718
Cingulate	31	−10	26	44	3.29	71	Posterior cingulate	31	4	−42	−44	2.98	64
Inferior frontal gyrus	44	−66	14	14	3.11	11	Cuneus	18	34	−58	−18	2.91	38
							Lingual gyrus	18	26	−78	−6	3.12	51
							Precentral gyrus	9	42	6	40	3.11	59
							Paracentral gyrus	5	2	−46	64	3.05	11
							Postcentral gyrus	3	10	−36	72	2.85	10
							Postcentral gyrus	3	56	−18	26	2.73	10
Participant 3													
Precentral gyrus	6	−62	2	36	4.16	124							
Inferior parietal lobule	40	−56	−46	56	3.63	24							
Precentral gyrus	4	−48	−18	40	3.15	21							
Middle frontal gyrus	9	−38	18	−36	2.84	12							
Participant 4													
Angular gyrus	39	−48	−78	42	3.62	454	Cerebellum	–	2	−64	−18	2.82	47
Inferior parietal lobule	40	−66	−34	48	3.27	67							
Middle temporal gyrus	21	−64	−40	−2	3.07	108							
Cerebellum	–	−8	−66	−30	3.01	44							
Precuneus	19	−36	−90	46	2.79	14							
Inferior parietal lobule	40	−66	−36	24	2.71	20							
Participant 6													
Caudate	–	−11	−4	25	2.58	39							
Less successful responders													
Therapy-induced Naming													
Participant 5													
Cingulate	31	−10	42	32	5.01	8098	Middle frontal gyrus	9	30	36	40	2.81	8098
Middle temporal gyrus/supramarginal gyrus	39/ 40	−46	−72	18	4.92	3018	Cuneus	19	32	−86	26	3.00	14
Precentral gyrus	6	−52	0	40	3.05	28	Precuneus	31	22	−76	24	2.76	26
Participant 7													
Postcentral gyrus	2	−34	−44	78	4.35	638	Superior temporal gyrus	22	58	−56	−14	4.45	24
Medial frontal gyrus	6	−6	−30	82	3.14	29	Postcentral gyrus	7	18	−54	78	3.47	143
Superior frontal gyrus	9	−14	56	22	3.05	20	Superior parietal lobule	7	32	−60	70	3.37	33
Precentral gyrus	6	−24	−22	80	3.05	59							
Participant 8													
Supramarginal gyrus	40	−50	−54	24	2.96	73	Precentral gyrus	4	64	−14	36	3.62	347
Cerebellum	–	−16	−48	−14	2.76	28	Precentral gyrus	4	38	−16	38	2.80	20
							Cingulate gyrus	32	16	28	28	2.79	39
Participant 9													
Fusiform gyrus	18	−28	−86	−24	3.06	38	Lingual gyrus	18	16	−90	−22	3.92	434
							Parahippocampal gyrus	36	30	−14	−30	3.79	60
							Inferior frontal gyrus	47	54	26	−14	3.19	56
							Cuneus	17	12	−98	−10	3.08	23
							Precuneus	7	2	−78	56	2.89	21
							Medial frontal gyrus	10	16	60	8	2.89	21

areas that would predict greater improvement. For instance, Richter, Miltner, and Straube (2008) reported activation in the right PCG, but also showed that this area predicted therapy-related behavioural improvement. In a recent study, Fridriksson (2010) used a regression analysis to show that the left precentral gyrus, pars opercularis and the inferior and superior parietal lobules were associated with greater behavioural improvements. In the present study, we also found a positive correlation between naming improvement and activity in the left PCG, both before and after therapy. These results suggest that the left PCG could play an important role in the recovery from chronic aphasia, especially when using SFA. Interestingly, this area is already known to play a role during overt naming in healthy controls, but not during covert naming (Shuster & Lemieux, 2005). As pointed by Pulvermüller et al. (2006), the PCG includes the primary motor and premotor cortices, and it has been associated with the articulation of speech (Pulvermüller et al., 2006). However, the activation of the left PCG has also been reported in a pseudoword reading task (e.g., Brunswick, McCrory, Price, Frith, & Frith, 1999) and in lexical decisions on pseudowords (Price et al., 1994). We can therefore hypothesize that this area may play a role not only in speech programming but also in language processing. Since its activity was associated with better naming ability following SFA therapy, this seems to be a good predictor of naming improvement.

Although no relationship was detected between lesion size and the degree of improvement, we found a lesion in Broca's area (BA45) to be a negative predictor of naming improvement in our group of participants using patient lesion-deficit mapping. Thus, it appears that the specific location of a brain lesion is a better predictor of therapy outcome than its size (Dronkers et al., 2004;

Kertesz, Lau, & Polk, 1993; Meinzer et al., 2010; Naeser et al., 1987; Naeser & Palumbo, 1994; Parkinson et al., 2009). This suggests that the identification of preserved brain areas after brain insult could be a useful predictor for therapy-induced improvement. The role of Broca's area in language processing has been reported on extensively; specifically, the pars triangularis (BA45) of Broca's area contributes to lexico-semantic control and retrieval processes (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Miceli et al., 2002). Previous studies have shown that semantic encoding is associated with selective activation of the left IFG (BA45/46) (Demb et al., 1995). Considering that SFA therapy focuses on the activation of the most distinguishing semantic features in order to select the target word and then retrieve its phonological form (Boyle, 2004), it is not surprising that a lesion in brain areas involved in semantic encoding and lexical retrieval is a negative predictor of improvement following SFA. Conversely, our results differ from those of Fridriksson (2010), who showed that patients with lesions in the left middle temporal lobe and temporal-occipital junction were those who improved the least following cueing hierarchy therapy (Wambaugh, Cameron, Kalinyak-Fliszar, Nessler, & Wright, 2004; Wambaugh et al., 2001). These contradictory results can be explained in two ways. First, the nature of the therapy was different: in both cases, a set of cues was provided to the patients, but the cues used by Fridriksson (2010) were both semantic and phonological and did not specifically target semantic prompts, as is the case in SFA therapy. It is also true that given the number of participants, we cannot ascertain that only damage to Broca's area predicts patients' response to SFA; however, this area survived a 1% false discovery rate to control for multiple comparisons, which suggests that the preservation of Broca's area could be a useful predictor of SFA therapy efficacy. Further studies would need to confirm these results with a larger number of patients, but this is a first attempt to identify key areas for efficient intervention with SFA. Identifying preserved brain areas that predict response to specific therapy approaches may one day inform clinicians on appropriate therapy choice, so that the potential for aphasia recovery could be increased.

Second, and probably most importantly, all the patients in our study were non-fluent, except one (P08; 88.9% of the participants), whereas 14 out of 26 patients (53.4%) in Fridriksson's (2010) study were fluent. In this regard, patients with fluent aphasia have shown greater improvements when the left temporal lobe was well preserved (Gainotti, 1993). Thus, the contradiction between our results and Fridriksson's (2010) could be explained by the typology of the patients recruited in each study.

Regarding the individual neuroimaging results as a whole, the MSR group showed a contraction of the adaptive network and no significant post-therapy RH activations compared to pre-therapy activation maps. Conversely, the LSR group showed more activation clusters and RH activations following therapy. This dissociation suggests that the different post-therapy activation patterns in MSR and LSR may relate to different levels of therapy success across groups. Better improvements, in terms of accuracy and rapidity, have been associated with either the greater efficiency of the initial strategy or the use of a new strategy (Jonides, 2004). In complex cognitive functions, a decrease of activation is associated with a more efficient neural network (Kelly & Garavan, 2005). In this regard, Cardebat et al. (2003) showed that improvement in word generation performance was reflected by a contraction of activations. This decrease in activation has also been shown in motor overtraining (Münte, Altenmüller, & Jäncke, 2002), which resulted in improved performance. In line with this evidence (Cardebat et al., 2003; Münte et al., 2002), the present results could suggest that the naming strategy induced by SFA considerably improved word retrieval efficiency in the MSR group, which resulted in less need to recruit areas to support the naming task. Conversely, the LSR group may have improved their naming abilities by adding more resources, but did not restore more 'normalized' processes (Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007) or more efficient language strategies (Richter et al., 2008). The LSR group showed a larger number of activated areas following SFA but included more processing areas that are not specific to language, such as the lingual gyrus and the cuneus.

Regarding the behavioural results, all participants benefited from SFA therapy. Previously, studies reporting on SFA therapy in aphasia (Antonucci, 2009; Boyle, 2004; Boyle & Coelho, 1995; Marcotte & Ansaldo, 2010) included no more than three patients. This is the first study to report on SFA therapy effects in a larger group of chronic patients with aphasia. We report two distinct patterns across participants: one group improved more and in a smaller number of sessions (MSR), whereas the other improved less in a larger number of sessions (LSR). Unlike lesion size, premorbid language abilities showed strong correlations with naming improvement. Our results are in line with previous evidence (Lazar et al., 2010) showing the predictive value of pre-therapy naming, repetition and comprehension abilities, in the recovery from aphasia. Thus, Lazar et al. (2010) showed a strong correlation between the initial severity of naming, comprehension and repetition impairments, and the degree of recovery from mild to moderate aphasia in the first three months (Lazar et al., 2010). As in Lazar et al. (2010), we found a strong correlation between response to SFA and the pre-therapy score in naming and comprehension deficits; a less strong correlation was observed with repetition. This relationship between initial severity and improvement has also been shown in global aphasia, and is claimed to be the main factor in predicting the final outcome (Mark, Thomas, & Berndt, 1992). The present results support the earlier evidence. Even in the chronic phase of aphasia, naming, comprehension and repetition measurements prior to SFA therapy were good predictors of therapy outcomes. However, although improvements were more modest in the LSR group, these patients benefited from SFA as well. In cases of severe aphasia, increasing the expressive vocabulary by 12 to 15 words is still clinically significant and can make an important change in daily communication needs when the words are well targeted. This means SFA can still be a good therapy choice for the patients with lower comprehension and naming scores prior to training, though the expected naming improvement is not as large.

From a methodological point of view, the use of covert versus overt naming tasks is a major issue in neuroimaging studies of language. One major problem with the use of overt naming tasks is the induction of movements and artefacts, which could lead to false-positive activations or even mask brain activations (Barch et al., 1999). It is widely believed that covert and overt naming are different only in terms of the speech production of the word. Because of this trend, many studies have used covert naming and have discussed naming in general. However, studies that have used fMRI have shown that overt and covert naming tasks do not in fact activate the same cortical areas (e.g., Barch et al., 1999; Shuster & Lemieux, 2005). Moreover, the ultimate goal of language therapy in patients with aphasia is the overt production of words that they were not able to name before therapy. Many of the participants may be able to access some semantic information but not to retrieve the phonological form of the word. Thus, by using a covert naming task, we would be unable to distinguish between correct naming and incorrect naming, which characterizes both anomia and paraphasias. In order to minimize these artefacts, the use of an event-related paradigm (Shuster & Lemieux, 2005) and standard head fixation with cushions placed in the birdcage head coil (Heim, Amunts, Mohlberg, Wilms, & Friederici, 2006) aimed to minimize these controversial issues in the present study.

Before concluding, one potential shortcoming of the present study is the lack of a comparison task to control for effects that are not specific to therapy. Stability of performance and brain activation across repeated fMRI scans has already been demonstrated in object naming in chronic aphasia (Fridriksson et al., 2006). Moreover, overt naming tasks are considered to involve minimal practice effects that could account for differences in activation patterns (McGonigle et al., 2000), and thus are suitable for longitudinal studies (Meltzer, Postman-Caucheteux, McArdle, & Braun, 2009). However, the functional changes may also be related to a practice effect (Cardebat et al., 2003), with no implications regarding the nature of the therapy administered. Further studies could explore the impact of SFA on an alternative task involving semantic processing, to determine whether this kind of therapy does or does not induce learning of a semantic strategy.

In conclusion, this study shows that SFA therapy significantly improved naming abilities several years after the aphasia onset. Despite the heterogeneity of the aphasia sample, group analyses were able to identify key areas recruited by SFA therapy that are also associated with successful improvement. Therapy-induced brain plasticity allowed for the recruitment of the left IPL, which supports the idea that fMRI is a suitable technique to investigate the effect of a language therapy in aphasia. The importance of the LH has been highlighted in other studies (Fridriksson et al., 2010; Meinzer et al., 2007; Postman-Caucheteux et al., 2010; van Oers et al., 2010), and the present results add a further piece of evidence in favor of the role of the LH in the optimal recovery from aphasia. As hypothesized, activation of perilesional areas in the LH was associated with a greater improvement.

If key areas that are recruited by specific therapy, such as SFA, can be identified, the potential for aphasia recovery will be dramatically increased by their stimulation. Two research groups have used group results to design a treatment that couples traditional aphasia therapies, transcranial direct current stimulation (Baker et al., 2010) and transcranial magnetic stimulation (Naeser et al., 2005; Naeser et al., 2010). Following the present results, it would be interesting to study the role of the left IPL and left PCG in SFA using either direct current stimulation or repetitive transcranial stimulation. Finally, functional connectivity analyses could also shed light on and help to better understand naming improvements following SFA in chronic aphasia.

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